

MAILSTOP: AMENDMENT  
PATENT  
2503-1190

IN THE U. S. PATENT AND TRADEMARK OFFICE

In re application of

Ezio BOMBARDELLI Conf. 7306

Application No. 10/563,980 Group 1655

Filed February 27, 2006 Examiner M. McCormick

COMBINATIONS OF VASOACTIVE AGENTS AND THEIR USE IN THE  
TREATMENT OF SEXUAL DYSFUNCTIONS

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents October \_\_\_\_\_, 2008  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Ezio BOMBARDELLI, the undersigned, an Italian citizen,  
residing at Via Gabetta, 13, 27027 Groppello Cairoli, Pavia -  
Italy, do hereby declare:

1. I have a degree in Biology from the University of  
Pavia.

2. I am currently consultant as President of the  
Scientific Board, Research and Development of Natural Products  
at INDENA S.p.A. - Viale Ortles, 12 - 20139 Milano - Italy,  
[which is the assignee of the instant application], and I am  
conducting research in medicinal plant derivatives. I am a  
member of the Italian Chemical Society, Fédération  
Internationale Pharmaceutique (F.I.P.), Gesellschaft für  
Arzneipflanzenforschung and Phytochemical Society of Europe.

3. My curriculum vitae is attached herewith.  
4. I am the inventor of the above-identified application.

5. I have reviewed the file history of application Serial No. 10/563,980, including the specification, claims, and the Office Action mailed June 5, 2008.

In doing so, I have reviewed the rejection of claims 1, 4, 6 and 9 under 35 U.S.C. § 103(a) as allegedly being obvious over BOMBARDELLI et al. (EP 0693278) and NISHIZAWA (JP 09157136) set forth on pages 5-7 of the Office Action.

I have also reviewed the rejection of claims 1, 3-4, 6 and 9 under 35 U.S.C. § 103(a) as allegedly being obvious over DI PIERRO (WO 02/098436 A) and DWEEK (1999) in view of BOMBARDELLI (U.S. 5,376,371) as set forth on pages 7-9 of the Office Action.

6. Based on my review of the application and given the knowledge in the art at the time of the invention, it is my opinion that the combined teachings of (1) BOMBARDELLI et al., and NISHIZAWA, and of (2) DI PIERRO, DWEEK (1999) and BOMBARDELLI (U.S. 5,376,371), do not render obvious the invention of claims 1, 3-4, 6 and 9 as the claimed invention achieves surprising and unexpected results indicative of non-obviousness.

The claimed combination of ingredients is able to increase sexual performances, especially in women, as can be seen in the test carried out on female volunteers (see page 5, last paragraph to page 6 of the PCT application, published

WO2005/004890 to which the instant application is a National stage application). The active ingredients making up the claimed composition were unexpectedly found to behave synergistically, as can be seen in the experiments discussed below.

For comparative purposes, 20 women aged from 35 to 45 having normal sexual activity were topically treated with 0.2 ml of a gel formulation, as follows:

Group 1: control (placebo)

Group 2: gel containing 1% esculoside

Group 3: gel containing 2% ethyl ximenynate

Group 4: gel containing 0.2% purified extract of coleus > 80%

Group 5: gel according to example 1 of the present application.

The hemodynamic of vulvar mucosa was examined by means of laser-doppler flowmeter at time 0 and after 30 and 60 min from the topical application of the formulation (Sarrel Ph. M. and Brinda W, *Fertility and Sterility*, 68, 6, 1997).

The results are reported in the following Table:

Treatment	Flow in the vulvar mucosa (mV) (M±S.E.)		
	Basal	30min	60min
Group 1	231±25	228±31	241±30
Group 2	241±33	244±29	263±30
Group 3	235±28	253±30	271±43
Group 4	239±26	244±33	289±36
Group 5	250±31	375±29**	473±41**

\*\*p<0.001 Split-plot Anova

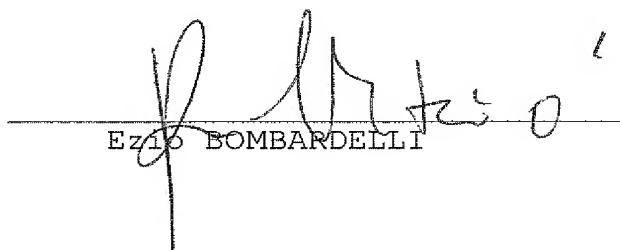
These results demonstrate that the composition according to the instant application strongly increases the hematic flow in the vulvar mucosa 30 min after topical application and reaches the maximum effect at 60 min.

On the contrary, each single component (by itself) only caused a slight increase of the hematic flow at each time point and the sum of the individual effects is significantly lower than the increase observed in Group 5 (which corresponds to the claimed invention).

Based on this evidence, it is opinion that the combined ingredients of the composition, according to claims 1-9, behave synergistically to achieve a surprising and unexpected property over the compounds in the combined prior art teachings and that such results are indicative of the nonobviousness of the claims.

7. I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: \_\_\_\_\_

  
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Ezio BOMBARDELLI

Attachments:

1. Curriculum vitae

**DR. EZIO BOMBARDELLI, B.Sc.**

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**J O B D E S C R I P T I O N**

**INDENA SpA** 1986 - present

MILAN ITALY

PRESIDENT OF THE SCIENTIFIC BOARD. RESEARCH AND DEVELOPMENT OF NATURAL PRODUCTS

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**INVERNI DELLA BEFFA SpA** 1966 - 1985

MILAN ITALY

DEPUTY DIRECTOR OF RESEARCH AND DEVELOPMENT. MAIN DUTIES WERE CONDUCTING CHEMICAL RESEARCHES ON NATURAL PRODUCTS OF NATURAL SEMI-SYNTHETIC ORIGIN. ISOLATION, STRUCTURE ELUCIDATION, SYNTHESIS AND MEDICINAL CHEMISTRY.

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**UNIVERSITY OF MILAN** 1962 - 1966

MILAN ITALY

ASSISTANT PROFESSOR AT THE BIOCHEMISTRY INSTITUTE

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**E D U C A T I O N**

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EUROPEAN PHYTOCHEMICAL SOCIETY

INTERNATIONAL PHARMACEUTICAL FEDERATION

AMERICAN CHEMICAL SOCIETY

MEMBER OF UNITED STATES PHARMACOPEIA

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**P U B L I C A T I O N S**

DR. BOMBARDELLI HAS PUBLISHED 381 SCIENTIFIC ARTICLES AND ABOUT 150 PATENTS. HE HAS PARTICIPATED TO MANY CONFERENCES AND SYMPOSIA WHERE HE HAS PRESENTED NUMEROUS SCIENTIFIC PAPERS.